FUNGUS DISEASES
# of the LUNGS

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FUNGUS DISEASES
# of the
LUNGS

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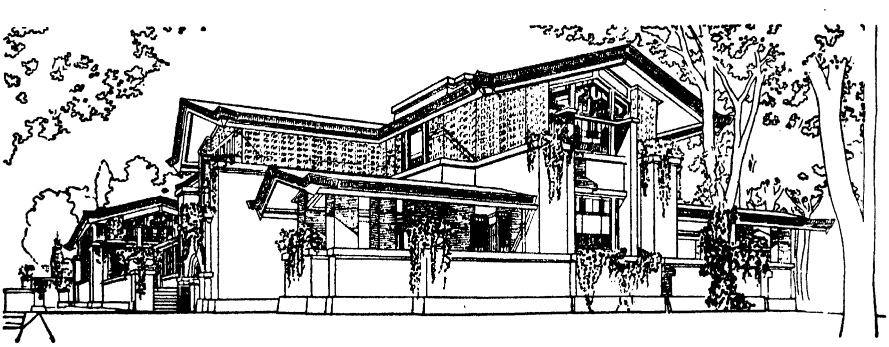

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FUNGUS DISEASES
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INTRODUCTION

For many years mycotic diseases of the lungs have been regarded as rare, exotic infections which were of interest to the esoteric specialist but did not concern the average general practitioner or internist. Evidence has been accumulated during the past ten years to change this point of view. We know now that *mycotic infections occur with sufficient frequency to justify their being considered in the differential diagnosis of every difficult and complicated pulmonary and systemic infection.*

Some of the mycoses such as moniliasis, cryptococcosis, geotrichosis and actinomycosis are endogenous infections, analogous to pneumococcus pneumonia, and may occur *at any time, in any climate* and *in any strata of society.*

Other mycoses, such as coccidioidomycosis, histoplasmosis, North American blastomycosis and South American blastomycosis, have *a fairly fixed geographic distribution.*

The infecting fungi obviously are present somewhere in nature, but whether they are primarily parasites of animals and plants or merely saprophytes in the soil has not been determined. Sporotrichosis, which is world-wide in distribution, is primarily a disease of plants, and man is an accidental and terminal host.

Coccidioidomycosis is endemic in the dry, sandy areas of the entire southwestern part of the country. Positive skin tests with coccidioidin have shown that 60 to 80 per cent of the inhabitants of certain areas have been infected with *Coccidioides immitis.* Additional studies have shown that there is a benign primary form of the disease which is very prevalent in these areas. The benign form of the disease occurs by the thousands, while the malignant, progressive, highly fatal form is numbered by the hundreds. Obviously, *it is important, in a difficult diagnostic problem, to know if the patient has made a visit, even a very brief one, to the arid Southwest.*

Histoplasmosis is another mycosis with a fairly definite geographic distribution. Three years ago the total number of proved cases numbered less than one hundred. As a result of the studies of Christie and his associates in Tennessee and of Palmer and his associates in Missouri, Kansas and Ohio, we know now that primary benign infections with *Histoplasma capsulatum,* or an antigenically related fungus, occur by the tens of thousands in the Mississippi Valley. These benign infections leave small calcified areas in the parenchyma of the lungs and in the hilar lymph nodes which are difficult, if not impossible, to differentiate from the calcium deposits that follow a primary infection with tuberculosis.

North American blastomycosis may be found anywhere on the continent of North America but occurs with the greatest frequency in the Mississippi Valley, across Tennessee and down into the Southeastern states with North Carolina as the center of the endemic area. The great prevalence of this disease has been demonstrated by the work of Conant, Martin, Smith, Baker and Callaway, of Duke University. If a benign primary form of blastomycosis occurs, it has not yet been recognized.

Of all the non-tuberculous infections, the mycoses most closely resemble tuberculosis. Disease-producing fungi grow slowly in the tissues; they induce giant cell formation and frequently produce a state of tissue hypersensitiveness which is analogous to that occurring in tuberculosis. Some of the mycoses, such as geotrichosis, moniliasis and aspergillosis, are relatively mild diseases; but others, such as actinomycosis, North and South American blastomycosis, coccidioidomycosis, cryptococcosis and histoplasmosis, have a mortality much higher than that of tuberculosis.

The discovery of a new antibiotic, tomatin, derived from wilt-resistant tomato plants, by Irving, Fontaine and Doolittle* offers some hope for a specific treatment for the yeast and mold-like fungi. Tomatin is effective in test tube experiments but is not yet sufficiently purified for use in man.

ACTINOMYCOSIS

Actinomycosis is the most common and the most widely distributed of the severe systemic mycoses. Ninety per cent of the cases are caused by the anaerobic *Actinomyces bovis* and approximately 10 per cent by species of the aerobic *Actinomyces* which are now called *Nocardia.* The differentiation between the two forms of actinomycosis depends upon the isolation and idendification of the particular fungus. The clinical course of the disease, the diagnosis and the treatment are the same for both types of infection.

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* Irving, G. W., Jr., Fontaine, T. D., and Doolittle, S. P.: Lycopersicin, A. Fungistatic Agent from the Tomato Plant. Science, 102: 9, 1945 (July 6).

That the patient's own mouth is the source of infection in pulmonary actinomycosis has been shown by recent work. Pathogenic actinomycetes have been found in the tonsils and about the teeth of apparently normal individuals. Such fungi are in a strategic position to invade the jaw locally, giving rise to cervical actinomycosis, to be aspirated into the lungs to initiate pulmonary infection, or to be swallowed and infect the intestines and abdominal organs.

Pulmonary infections with actinomycetes are usually bilateral and basal, but they may occur as a unilateral lesion in any part of the lung.

The *symptoms* in the first few weeks of the disease are those of a subacute pulmonary infection with a mild, irregular fever, cough and some expectoration. The sputum becomes mucopurulent and may contain blood as the disease progresses and small abscesses develop in the lung. Sometimes the infection begins in one or more ribs, invading both the lung and the subcutaneous tissues.

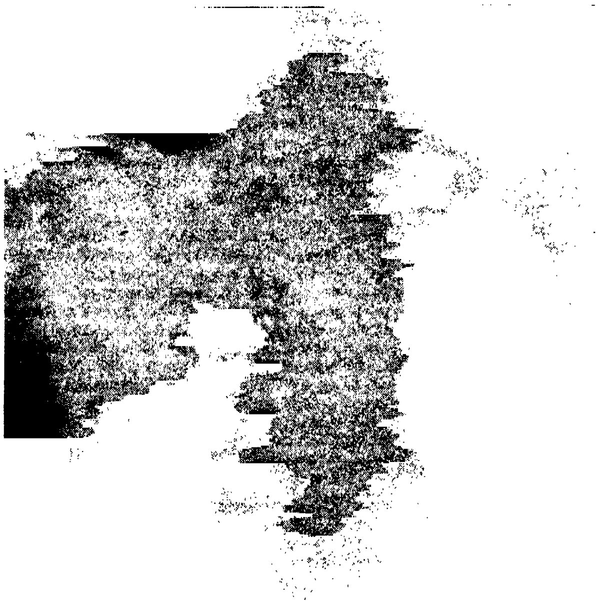

Figure 1. Actinomycosis, showing involvement of the right lung. The etiologic agent was the acid-fast *Nocardia asteroides*. Cured with sulfadiazine and potassium iodide. (After Benbow, Smith and Grimson, *American Review of Tuberculosis, 49*: 395, 1944.)

Pulmonary infections usually extend to the pleura, causing pleural pain. An occasional patient develops a pleural effusion, but the fungus more often invades directly through the pleura to the chest wall, giving rise to numerous draining sinuses. As the disease progresses, patients lose weight and strength and become anemic; they develop spiking temperature, night sweats, dyspnea and other signs of severe pulmonary disease. The infection may extend into the mediastinum, causing dysphagia, and at times there is an invasion of the pericardium and heart. The sedimentation rate is elevated, and there is an increase in the white blood count with a rise in the percentage of polymorphonuclear leukocytes. The physical signs in the early stages resemble those of tuberculosis except that the primary site of infection is more often at the bases of the lungs. As the disease progresses, massive areas of dulness appear and the chest wall may be retracted and limited in motion. The presence of subcutaneous abscesses or open draining sinuses should suggest the possibility of mycotic infection.

The *chest films* usually show smooth, irregular, massive areas of consolidation without cavity formation or with small, irregular areas of rarefaction. Although the lesions may appear in any part of the lung (Fig. 1), they are found most often in the lower lobes and are usually bilateral. Sometimes areas of massive consolidation project from the hilum and have the appearance of a neoplasm. In the advanced cases the pleura usually is involved with either massive pleural adhesions or massive accumulations of fluid which may or may not be encapsulated. The ribs are invaded frequently and usually show both destructive and proliferative changes.

The *diagnosis* is established by finding the typical "sulfur granules" or tangled masses of gram-positive branching filaments in the sputum. When subcutaneous abscesses are present, pus aspirated from unopened lesions should be examined directly for the fungus and cultured under both aerobic and anaerobic conditions. Species of aerobic *Nocardia* may be either partially acid-fast or completely non-acid-fast. When open, secondarily infected, draining sinuses are present in the chest wall, the inner layers of the gauze dressings should be examined under the low power of the microscope for the presence of "sulfur granules."

Actinomycosis presents a variety of clinical pictures, and it must be differentiated from tuberculosis, syphilis, neoplasm, tularemia, osteomyelitis and staphylococcic actinophytosis (botryomycosis), as

well as certain other mycoses, especially North American and South American blastomycosis, coccidioidomycosis, cryptococcosis and sporotrichosis.

The *prognosis* in pulmonary actinomycosis is grave. Before the discovery of sulfonamides and penicillin only about 25 per cent of the cases of pulmonary actinomycosis recovered following medical treatment with potassium iodide or after surgical drainage. The prognosis is much better with newer types of treatment.

The patient with pulmonary actinomycosis should have the same general supportive *treatment* as that given a case of tuberculosis, and the treatment should include, in addition to a good diet, extra vitamins, especially cod liver oil and fruit juices. All of the sulfonamides have been used successfully in the treatment of pulmonary actinomycosis. Sulfadiazine seems to be the drug of choice at the present time although the newer sulfamerazine has the theoretical advantages of slower absorption and slower excretion. Potassium iodide should be administered concurrently with the sulfonamide therapy. The sulfonamide blood level should be maintained between 5 and 10 mg. per cent. The potassium iodide is administered orally, using a saturated solution of the drug. The usual procedure is to give 3 drops t.i.d. p.c. in one-half ounce of water. The dose is increased either by one drop each day or 3 drops each day until the patient is receiving 20 drops t.i.d. After reaching 20 drops t.i.d., we have found it advisable to reduce the dose to 3 drops t.i.d. and then gradually increase it again to the maximum of 20 drops t.i.d. Occasionally it is necessary to give much larger doses, even up to 3 or 4 gm. per day. Sodium iodide intravenously in doses of 1 gm. per day may be substituted for the potassium iodide by mouth or may be used as a supplement.

In the usual pulmonary case there is adequate drainage through the bronchus; but if such is not obtained or if the infection has extended into the chest wall, surgical drainage is essential. Since the sulfonamides protect against many of the secondary infections, the surgeon can afford to be radical. All sinus tracts should be explored and drained, and the severely damaged tissues should be excised as far as it is practical. Lobectomy and pneumonectomy should be considered in selected cases which have failed to respond to other types of therapy.

Penicillin in doses as small as 10,000 units every three hours or 80,000 units per day frequently results in rapid elimination of fever and marked clinical improvement in the patient, but surgery and potassium iodide still must be used as supplementary treatment. We have seen cases where penicillin alone in daily doses of 100,000 to 200,000 units up to a total of three to four million units failed to cure patients when surgery and potassium iodide were neglected.

ERYSIPELOID

Pasteur isolated *Bacillus rhusiopathiae* from swine erysipelas in 1882. It is also found in the slime on both fresh and salt water fish. It causes disease in farmers, veterinarians, fishermen and fish handlers. True epidemics have been observed in bone button factories where raw pig bones were used in the manufacture of buttons. Most of the infections have been on the hands or in the eyes, but they may occur on any part of the body. The literature describing this disease has been collected by McGinnes and Spindle, Klauder and Harkins, and Klauder, Kramer and Nicholas. Sulfonamides and penicillin *probably* are effective in the treatment.

BACTEROIDES INFECTIONS

Bacteroides necrophorus causes necrotizing infections in animals. In 1945 Smith and Ropes reported 20 new cases and reviewed the literature. Septicemia, osteomyelitis, pulmonary abscess, subcutaneous abscess and meningitis have been described. There is no recognized treatment but sulfonamides, penicillin and streptomycin should be tried.

ACTINOBACILLOSIS

Actinobacillus lignieresi causes "lumpy jaw" in cattle. Cases of septicemia, suppurative bronchopneumonia and endocarditis have been found in man. The literature has been reviewed by Custis, Halley and Bacon in 1944. Potassium iodide is a specific for the disease.

STAPHYLOCOCCIC ACTINOPHYTOSIS (BOTRYOMYCOSIS)

Occasionally staphylococci produce chronic granulomatous lesions with definite granule formation which under the low power of the microscope resembles typical "sulfur granules." The clinical course of the disease resembles actinomycosis. The organism grows readily as an ordinary *Staphylococcus.* The treatment is surgical drainage supplemented by penicillin and potassium iodide.

NORTH AMERICAN BLASTOMYCOSIS

North American blastomycosis is characterized by the formation of granulomatous lesions in various parts of the body, but there is a marked predilection of the skin, lungs and bones. Blastomycosis is a relatively common mycotic disease. We have seen over 40 cases in North Carolina in the past 14 years. Except for an occasional case in Canada and England, the infection has been found only in the United States.

The disease is not spread from man to man, but evidently is derived from some source in nature. Two cases of spontaneous infections in dogs have been reported, and the serum from one of these dogs fixed complement with antigens prepared from human strains. Blastomycosis may occur in patients as young as six months or as old as 80 years, but in the series of 347 cases collected by Martin and Smith, more than 50 per cent were between the ages of 20 and 40. The disease occurs nine times as frequently in males as in females, and all races seem to be equally susceptible.

The infection may begin primarily in the skin and remain localized for months or years before it spreads to the internal organs. Most cases of systemic blastomycosis begin with pulmonary infection. In the fatal cases studied at necropsy, 95 per cent had pulmonary infections, and in more than half of the cases the most extensive lesions were found in the lungs. The bones were found to be infected in 60 per cent, with the vertebrae and ribs being involved most frequently. The liver, spleen and kidneys were invaded in about 40 per cent, the nervous system in about 30 per cent and the prostate in about 20 per cent. The lesions in the liver and spleen are usually quite small and these organs are not enlarged. The intestinal tract is spared in most instances.

The *onset* of pulmonary blastomycosis frequently is insidious. The symptoms may resemble those of an ordinary subacute respiratory infection with dry cough, some pain in the chest, slight fever and mild dyspnea. After a period of weeks or months the sputum becomes purulent and may contain blood. As the pulmonary infection progresses, the dyspnea becomes more marked, the fever is higher, there is a marked loss of weight and strength and the patient develops night sweats. The pleura may be involved and sinuses may appear in the chest wall, but this complication is much rarer in blastomycosis than in actinomycosis. The mediastinum frequently is invaded in the latter stages of the disease, and Baker and Brian have shown that the pericardium and heart may be involved. In the terminal cases with widespread dissemination, symptoms referable to other internal organs may appear, such as pain in the bones or prostate or paralysis from invasion of the brain and spinal cord.

The *physical signs* of pulmonary blastomycosis are similar to those of pulmonary abscess or massive tuberculosis. Percussion usually reveals dulness, but rales are inconstant and variable in type and distribution.

The *chest films* may show, in early cases, an enlargement of the mediastinal lymph nodes without obvious parenchymal lesions. In most instances, however, dense masses are seen. Such masses may be located near the hilum and project into the lung fields

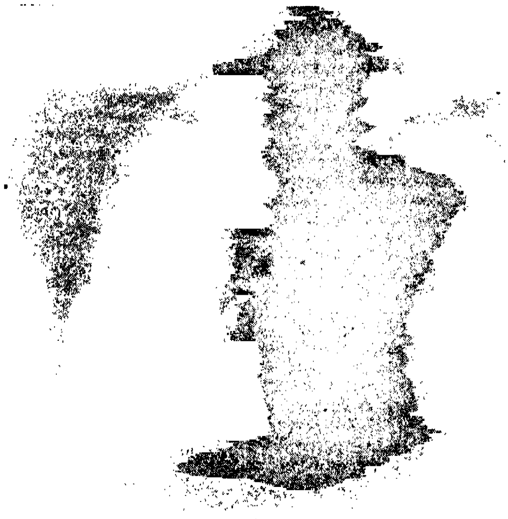

FIGURE 2. North American blastomycosis, showing hilar involvement and tumor-like masses projecting out into the lung fields. The patient was first desensitized with an autogenous *Blastomyces* vaccine and then treated with x-ray and potassium iodide. The shadow on the right disappeared completely, and the one on the left was reduced to a small linear scar. The patient was well 10 years later. (After Martin and Smith, *American Review of Tuberculosis, 39*: 488, 1939.)

with irregular outlines. This type of infection frequently suggests the diagnosis of neoplasm (Fig. 2), especially when the patient also has localized pain in the chest and blood in the sputum. We have seen three patients with pulmonary blastomycosis in whom the lung lesions were originally diagnosed incorrectly as carcinoma of the bronchus. In one of these cases lobectomy was performed, and the diagnosis of blastomycotic infection was made only after microscopic examination of the excised lung. Cavities are not characteristic and, when present, are usually small and have irregular, hazy outlines. Sometimes infection spreads through the body by way of the blood stream. The pulmonary shadows may then resemble miliary tuberculosis except that they are a little coarser and are not quite as well defined. When disseminated blastomycosis is suspected, x-rays should be made of the entire skeleton. As in tuberculosis, the bodies of the vertebrae may be destroyed, resulting in collapse with compression of the spinal cord. The lesions usually are less cyst-like than those seen in coccidioidomycosis and are more destructive and less proliferative than those of actinomycosis. In many instances, however, a differential diagnosis between these three diseases cannot be made from the films alone.

As the disease progresses, a hypochromic anemia develops; there is an increase in the sedimentation rate and an increase in the white blood count with a rise in the polymorphonuclear leukocytes.

A positive skin test to *Blastomyces* vaccine develops in the more extensive skin cases and in almost all of the systemic cases. The dying patient, however, may be anergic. Dr. Donald S. Martin, in our clinic, employs the complement fixation technique, using as the antigen either the whole bodies of the organisms or a powdered extract. The test frequently is positive in the progressive cases, but patients who recover eventually lose their antibodies and the tests become negative. A negative complement fixation test will not rule out the disease, but we have never seen a false positive.

The *diagnosis* is established usually by the demonstration of the typical organisms. The double-contoured, budding, yeast-like organisms may be found in the sputum or in pus from subcutaneous lesions, and can be grown readily on either Sabouraud's medium or meat infusion blood agar. The blood agar plates should be incubated at 37 degrees C. and the Sabouraud's tubes or plates at room temperature. On blood agar the fungus grows slowly and develops small but heaped, wrinkled, waxy colonies after two or three weeks' incubation. Microscopic examination shows the colonies to be composed of budding yeast-like organisms identical with those seen in the infected tissue. On Sabouraud's medium at room temperature the fungus develops a white, cottony aerial growth after two or three weeks which becomes slightly brownish or tan-colored on further aging. The white fuzzy type of growth can be reverted to the yeast-like stage by subculturing on blood agar at incubator temperature.

Blastomycosis of the skin can be *recognized clinically* without difficulty and the diagnosis confirmed easily by demonstrating the budding fungus in the minute abscesses which develop in the edges of the lesions.

Systemic blastomycosis must be differentiated from tuberculosis, syphilis, neoplasm, lung abscess, sarcoidosis, silicosis and osteomyelitis, as well as other fungus infections, especially coccidioidomycosis, actinomycosis, cryptococcosis, South American blastomycosis, sporotrichosis and moniliasis.

Systemic blastomycosis is nearly always fatal. Martin and Smith noted a mortality rate of 92 per cent in patients who had been followed for two years or longer. In evaluating prognosis, the immunologic data may be helpful. Death is to be expected in patients with a high complement-fixing antibody titer and a negative or slightly positive skin test. The prognosis is best in the hypersensitive patient without complement-fixing antibodies in his serum.

The patient with blastomycosis should be *confined to bed* and *given a good diet supplemented by vitamins.* Iodide therapy has been used for the treatment of blastomycosis since it was first introduced by Gilchrist. Martin and Smith have found that the patients who are hypersensitive to the *Blastomyces* vaccine frequently fail to improve after iodide therapy and occasionally grow rapidly worse with further extension of the infection.

A *skin test* should be done on every patient before iodides are administered. If the skin test is positive to the heat-killed *Blastomyces* vaccine, then the patient should be desensitized before iodide therapy is instituted. If the skin test results in an erythematous zone about 2 cm. in diameter, the vaccine should be diluted 1:100 dilution before being administered subcutaneously. A 1:1000 dilution should be used if the skin reaction is as large as 3 cm. in diameter. If the reaction is larger than this, it is unsafe to inject the vaccine unless diluted 1:10,000.

The initial dose should be 0.1 c.c. of the indicated dilution injected subcutaneously, and this dose should be increased by 0.1 c.c every other day, or three times a week, until 1 c.c. is injected. The procedure is then repeated, beginning with 0.1 c.c. of the next lowest dilution, until the undiluted vaccine is administered. It is important to keep the dose below that capable of producing severe local or general reactions. If either local redness or general systemic reactions occur, the vaccine should be discontinued for several days and then resumed, but beginning with an injection one-tenth as strong as that which produced the reaction. Some patients are never able to take even the 1:10 dilution without reaction. Complete desensitization is not necessary and is not to be expected.

Iodides can be started after about two weeks of vaccine treatment, but *it is essential that the drug be administered cautiously* and the rate of increase should be only one drop per day up to a maximum of 20 drops t.i.d. The dose should then be reduced to 3 drops t.i.d. and increased again to the maximum of 20 drops t.id. The dose should then be reduced to 3 drops t.i.d. and increased again to the maximum of 20 drops t.i.d.

If the patient has a negative skin test to the *Blastomyces* vaccine or gives a reaction less than 1 cm., the iodides may be administered by the rapid method——the initial dose being 5 drops t.i.d. with an increase of 3 drops each day up to a maximum of 40-60 drops t.i.d. Even larger doses may be given at times, as much as 3-4 gms.

Sodium iodide intravenously in doses of 1 gm. may be used as a substitute for or as a supplement to the potassium iodide.

Ethyl iodide inhalations have been employed successfully in some cases of blastomycosis. The drug is administered with an inhaler of the type made by the Warren Collins Instrument Company, of Boston, Mass. The initial dose, measured in the graduated centrifuge tube attached to the instrument, should be 0.25 c.c. three times a day. This may be increased by 0.25 c.c. every three or four days until the patient is taking as much as 1 c.c. t.i.d. The inhalation treatment may be combined with the oral administration of iodides.

Surgical drainage is indicated where there are large accumulations of pus. From observation of a limited number of cases, we have the definite impression that surgical measures should be deferred,

9. J'étudie le français depuis un mois.
10. J'étudie le français pendant une heure chaque[2] jour.
11. Nous allons à l'université chaque jour.
12. Je vais à l'université depuis trois ans.
13. Le professeur parle depuis une heure.
14. Généralement, un assistant prépare le matériel pour les expériences.
15. L'eau passe dans ce tuyau et après elle tombe dans l'éprouvette.
16. Nous pesons les objets sur une balance.[3]
17. L'observatoire de Paris existe depuis le XVII^{e} (dix-septième) siècle.
18. La classe de géologie va commencer.
19. Le professeur Lebrun va donner une conférence publique.
20. L'avion va partir dans cinq minutes.
21. Je vais acheter un dictionnaire scientifique.
22. Mon ami vient de[4] passer son examen.
23. Le train vient d'arriver.[5]
24. La conférence va bientôt commencer.
25. Le docteur Brun vient de publier un article intéressant.
26. Je viens de lire un compte rendu de la réunion.[6]
27. Mes amis vont à Paris mais je reste[7] à New York.
28. Les astronomes étudient les nouvelles photographies de la lune.
29. Nous venons de voir un excellent film documentaire.
30. Le Rhône traverse les Alpes puis il traverse le lac de Genève.
31. Le fer rougit[8] quand il est chaud.
32. Les flammes noircissent les pierres.
33. La lave noircit quand elle refroidit.
34. Au printemps les rivières et les torrents grossissent.
35. Je vais relire le premier chapitre de mon livre de français.
36. Les étudiants choisissent leurs cours[9] quand ils arrivent à l'université.
37. Cet appareil[10] mesure la vitesse du vent.

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[2] **chaque:** each, every. [Cf. **chacun, chacune:** each one, every one.]

[3] **la balance:** (pair of) scales; balance (*depending on context*).

[4] See §3.9.

[5] **arriver:** to arrive; to happen (*depending on context*).

[6] **la réunion:** meeting, get-together. [Cf. **réunir:** to reunite, to gather; **se réunir:** to meet, to get together.]

[7] **rester:** to stay, to remain. [Cf. **se reposer:** to rest; **le reste:** rest, remainder.]

[8] **rougir:** to blush, to turn red (*depending on context*). [Cf. **rouge:** red.] Note that most verbs deriving from adjectives belong to the second conjugation (-*ir* verbs): **noircir:** to blacken; **noir, -e:** black; **refroidir:** to cool; **froid, -e:** cold; **grossir:** to fatten; to increase; **gros, grosse:** big, heavy.

[9] **le cours:** course. [Cf. **la course:** race; **la cour:** court.]

[10] **l'appareil:** (*m.*) apparatus, machine, instrument, works.

and lungs; and *fourth,* a mixed type which involves both skin and internal organs.

Many of the skin and mucosal lesions resemble cutaneous leishmaniasis. Some simulate the dermal lesions of North American blastomycosis. The lymph nodes are involved much more frequently in South American blastomycosis than in North American blastomycosis.

In contrast to North American blastomycosis where pulmonary lesions are usually present, involvement of the lungs in the South American disease is *relatively late* and not a striking part of the clinical picture. The lungs are reported as being involved in 20 per cent of the patients with the visceral type of infection. The patient may have cough and purulent sputum which occasionally is blood streaked. Rales may be present throughout the lungs, but the lesions are rarely extensive enough to cause dulness to percussion.

The diffuse nodular appearance of the pulmonary lesions, as seen in x-ray (Fig. 3) and in postmortem studies, suggests that the fungus invades the lungs secondarily by the hematogenous route.

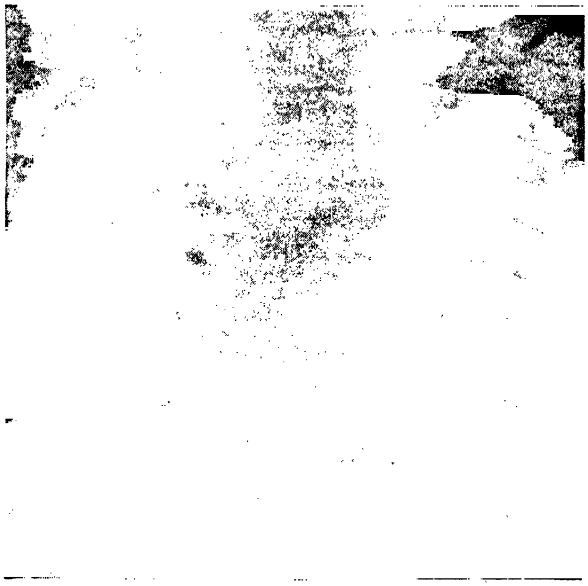

Figure 3. South American blastomycosis, showing extensive patchy infiltration throughout both lungs. There are some thin-walled cavities at the right base and definite enlargement of the hilar lymph nodes. (Courtesy of Dr. F. de Almeida, Sao Paulo, Brazil.)

Small thin-walled cavities may be present but extensive cavity formation is rare.

The diagnosis can be suspected from the appearance of the dermal and mucosal lesions, but must be confirmed by biopsy and culture. *Blastomyces brasiliensis* grows on blood agar at incubator temperature and on Sabouraud's medium at room temperature, producing colonies which resemble very closely those of *Blastomyces dermatitidis.* The mycologic diagnosis is established by demonstrating multiple buds on the yeast-like organisms found on the blood agar cultures.

The cutaneous and mucocutaneous lesions of South American blastomycosis must be differentiated from those of cutaneous leishmaniasis, yaws, syphilis, tuberculosis and certain neoplasm. The lymphatic and visceral types may be confused with visceral leishmaniasis, tuberculous adenitis and peritonitis, syphilis, neoplasms, aleukemic leukemia and Hodgkin's disease. Other mycoses such as histoplasmosis, coccidioidomycosis, actinomycosis, North American blastomycosis, cryptococcosis and sporotrichosis must be eliminated.

Before the introduction of sulfonamides the disease was invariably fatal. De Almeida has reported some improvement in early cases with iodide therapy, but he has observed that the iodides may accelerate the spread of the infection when the patient is already in an advanced stage of the disease. The importance of desensitizing hypersensitive patients before the administration of iodides has already been discussed in connection with North American blastomycosis.

At the present time Dr. Domingos de Oliveira Ribeiro and others in Brazil are *treating* this mycosis with sulfapyridine and sulfadiazine. The patients are given 2-4 gms. a day for many months. There is a dramatic improvement in the general condition of the patient. Unfortunately, however, many of these patients subsequently relapse and die of the disease. It is possible that desensitization with a vaccine carried out concurrently with the sulfonamide might give better results.

GEOTRICHOSIS

Geotrichosis is caused by one or more species of the genus *Geotrichum.* The fungus produces lesions in the mouth, intestinal tract, bronchi and lungs. This mycosis is not very common and frequently produces relatively mild infections. Certain forms of *Geotrichum* may be confused with *Blastomyces dermatitidis* which causes the highly fatal North American blastomycosis.

It is probable that this infection is endogenous in origin since the fungus frequently is found in the mouths and intestinal tracts of normal individuals. In a series of 314 stool specimens obtained from medical students, nurses and patients without intestinal symptoms, Schnoor cultured *Geotrichum* in 29 per cent.

Bronchial geotrichosis is the most frequently recognized form of the infection. The patient has symptoms which are identical with those of the ordinary chronic type of bacterial bronchitis. The sputum frequently has a peculiar mucoid or gelatinous consistency but only occasionally is blood streaked. There is little, if any, elevation of the temperature or pulse, and the general health of the patient is not affected seriously although he is handicapped by the harrassing cough. Physical examination shows numeorus medium and coarse rales, especially at the bases. Chest films show a diffuse peribronchial thickening which is accompanied sometimes by fine mottling at the bases of the lungs or in the midlung fields.

Pulmonary geotrichosis simulates tuberculosis, with an elevation of temperature, pulse and respiration and leukocytosis. The sputum is generally light in color and mucopurulent in contrast to the greenish, purulent sputum of tuberculosis. Frank hemoptyses may occur. The organisms are present in abundance in the purulent or bloody sputum and can be cultured without difficulty on Sabouraud's medium. On physical examination there is usually dulness and altered breath sounds with fine and medium rales resembling those found in acute reinfection tuberculosis. The x-rays show smooth, dense patches of infiltration which may or may not contain thin-walled cavities. The lesions may occur in any part of the lungs, but are sometimes confined to the upper lobes (Fig. 4).

The disease may be suspected from the presence of the peculiar mucoid, gelatinous sputum, but the *diagnosis* cannot be established without the demonstration of the organism both by direct examination and by culture. Direct examination is essential because occasional colonies of *Geotrichum* may be found in cultures of oral secretions from normal individuals. After some of the sputum is treated with a drop of 10 per cent potassium hydroxide and examined directly under the microscope, the fungus will be found as

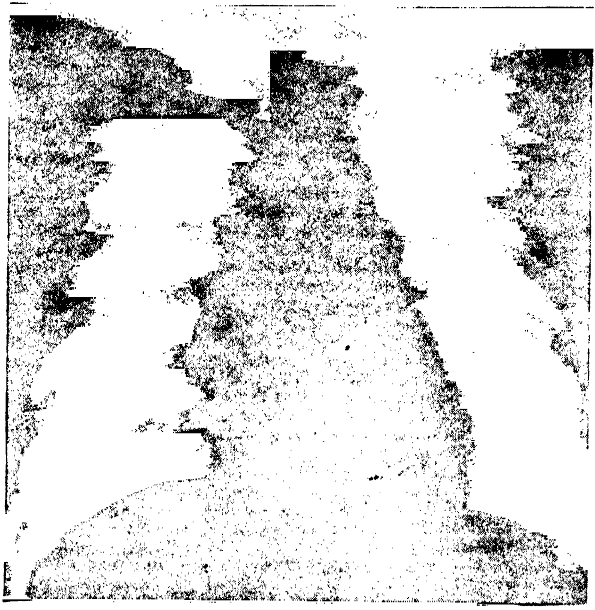

FIGURE 4. Geotrichosis of the lungs, showing two small cavities in the right upper lobe and a larger one in the left upper lobe. The lesions disappeared with potassium iodide therapy. (After Smith, *Journal of Thoracic Surgery, 3*: 241, 1934.)

oblong or rectangular cells 4 by 8 μ with somewhat rounded ends or as large spherical cells 4 to 10 μ in diameter. *Geotrichum* grows readily on Sabouraud's glucose agar at 37 degrees or at room temperature. The appearance of the growth is quite different, depending upon the temperature of incubation. At room temperature most of the growth is down into the medium and the long hyphae develop septal walls and then break up into rectangular arthrospores. These rectangular cells usually germinate by a germ tube from one corner, which is a characteristic method of growth for cultures of *Geotrichum*. At 37 degrees C. the colony is smaller and grows more on the surface of the medium. Short mycelia are produced with many more spherical cells 4 to 12 μ in diameter. Some of these spherical cells have rather thick walls and may be confused with the budding form of *Blastomyces dermatitidis,* but the presence of rectangular arthrospores establishes the diagnosis of geotrichosis.

Geotrichosis must be differentiated from tuberculosis, bacterial infection of the lungs and certain other mycoses, particularly moniliasis, North American blastomycosis, cryptococcosis and coccidioidomycosis. *Geotrichum* is not infrequently found in the sputum in association with Friedlander's bacillus, and it is often impossible to determine which organism is the primary invader. We have studied one patient with a chronic non-tuberculous infection of the lungs of 20 years' duration who has had in her sputum for over five years both Friedlander's bacillus and a species of *Geotrichum*. *Geotrichum* may be a secondary invader in pulmonary tuberculosis. In one patient with a mottled disease of the right upper lobe, *Geotrichum* was present in abundance in the sputum by direct examination and culture and no tubercle bacilli could be demonstrated even by guinea pig inoculation. Treatment with potassium iodide eliminated the cough and expectoration, but six months later her symptoms returned and tubercle bacilli without *Geotrichum* were found in her sputum.

The *prognosis* usually is good with geotrichosis. One of the chief reasons for recognizing this infection as a specific entity is to avoid confusing geotrichosis with North American blastomycosis in which the prognosis is poor.

The bronchial form of the disease responds readily to *treatment* with potassium iodide given by the rapid method described in the section on North American blastomycosis. The pulmonary form of the disease should be treated by the same regimen employed in tuberculosis, including rest in bed and a high vitamin diet. A thorough study of the sputum for the presence of tubercle bacilli, including guinea pig inoculation, should be made before iodides are administered. An autogenous vaccine should be tried if the patient does not respond to treatment with iodides.

COCCIDIOIDOMYCOSIS

Coccidioidomycosis, caused by *Coccidioides immitis,* produces two different clinical types of infecton. Cases of primary coccidioidomycosis occur by the tens of thousands in the arid regions of the southwestern part of the United States. The infection is an acute but benign, self-limiting respiratory disease. Approximately 1 per cent of the primary cases develop into progressive coccidioidomycosis which is a chronic, malignant, disseminated disease involving the cutaneous, subcutaneous, visceral and osseous tissues.

Emmons discovered that coccidioidomycosis is an endemic disease of rodents in the arid regions of the Southwest. The organism obviously is present in the dust and soil of these areas and may be introduced into the skin following an injury, but more often it is breathed into the lungs of men and animals with dust particles. Naturally occurring infections have been found in cattle, sheep and dogs, but there is no evidence that man acquires the disease directly from either human or animal sources.

The *symptoms* of primary pulmonary coccidioidomycosis resemble those of a mild upper respiratory infection although occasionally they are much more severe and simulate a lobar or lobular pneumonia (Fig. 5). An epidemic which occurred in a group of 75 soldiers was reported in detail by Goldstein and Mc-

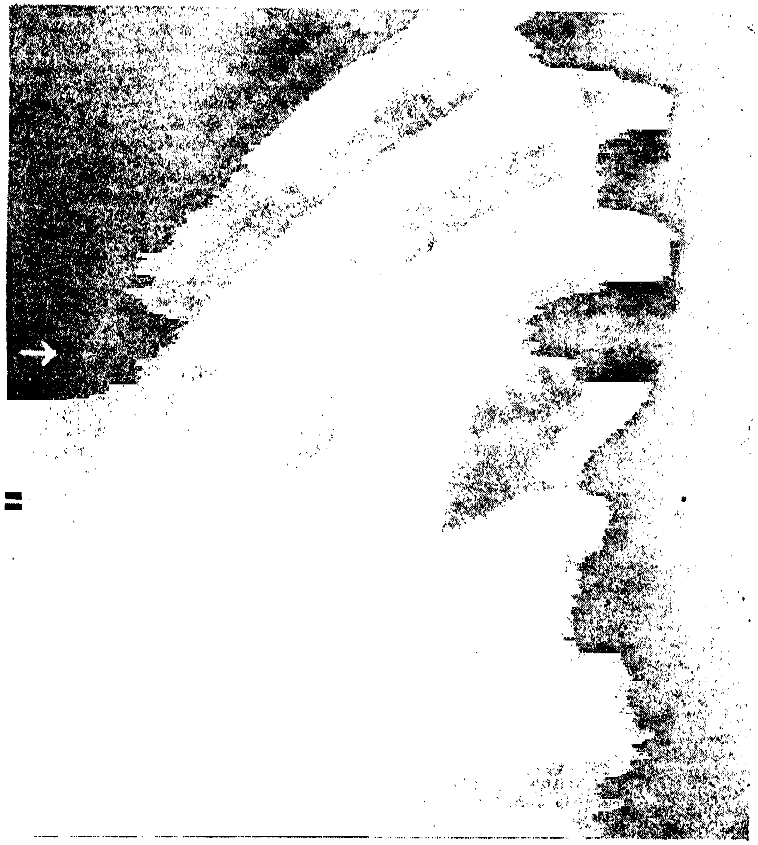

FIGURE 5. Primary coccidioidomycosis, showing soft nodular lesions which were found 13 days after a known exposure to dust containing arthrospores of *Coccidioides immitis* and 4 days after the sudden onset of symptoms. (After Powers and Starks, *Radiology, 37*: 448, 1941.)

Donald. The incubation period varied from one to three weeks. Fever was present in 100 per cent, cough 88 per cent, pain in the chest 88 per cent, chills 66 per cent, sputum 65 per cent, sore throat 37 per cent and hemoptysis 18 per cent of these patients. *Physical signs* were present in only 26 per cent, and these were largely limited to alterations in breath sounds. Dulness to percussion and rales were rare. In this series, erythema nodosum developed in 19 per cent, erythema multiforme in 2.6 per cent, morbilliform rash over the trunk and lower extremities in 4 per cent and arthralgia in 28 per cent. These *allergic reactions* appeared in 8 to 14 days after the onset of symptoms and usually were accompanied by eosinophilia. In a few instances the initial symptoms were those of pleurisy with effusion, but more often the dry type of pleurisy developed with severe pain in the chest.

Colburn made *x-ray studies* of the 75 soldiers with primary pulmonary coccidioidomycosis reported by Goldstein and McDonald. Although severe clinical symptoms were present, there were no detectable x-ray changes in 4 per cent of this group. Fan-shaped densities extending out from enlarged hilar nodes were present in 38.7 per cent. These shadows required an average time of 40 days for resolution although the extremes were 15 and 90 days respectively. In 24 per cent hilar lymph nodes were present without detectable parenchymatous lesions. In an additional 26 per cent there were both peripheral and sublobular infiltrations which occurred in the upper and lower lobes. Thin-walled pulmonary cavities, which are characteristic of the disease, developed in only 4 per cent. Some of these cavities healed in 60 days and some in 95 days, while others persisted. Cavities of this kind have been known to persist for years.

Occasionally calcification occurs both in the periphery of the lungs and in the hilar lymph nodes. These calcifications are difficult, if not impossible, to differentiate from calcifications which follow a primary infection with the tubercle bacillus. Cox and Smith have shown that *C. immitis* can be recovered from calcified foci many years after the initial infection.

Occasionally spherules containing the typical endospores can be found by direct examination of the sputum. The organisms grow readily in the mold-like form when cultured on Sabouraud's medium, although they may not have been demonstrated by direct examination of the fresh sputum. A positive skin test to coccidioidin appears after ten days to two weeks. The standard dose is 0.1 c.c. of a 1:1000 dilution of a standardized coccidioidin. If extreme sensitivity is suspected, the initial dose should be 0.1 c.c of a 1:10,000 dilution. The tests are read in the same manner as a tuberculin test. Precipitins and complement-fixing antibodies are absent in mild cases but may appear in the severe primary infections, only to disappear with recovery. In some of the patients with persistent cavities the complement-fixing antibodies may remain at a low level.

Among the soldiers studied in the Southwest, only about 0.2 per cent of the cases of primary infection in the Caucasian race proceeded to the development of the progressive, and usually fatal, form of the disease. It has been estimated that Negroes, Mexicans and Filipinos are about 20 times as likely to develop the progressive form of the disease as are representatives of the Caucasian race.

In many instances the primary form of the disease develops directly into the progressive form. If fever persists and new lesions appear in the parenchyma of the lungs or if subcutaneous or bone lesions occur, the diagnosis of the progressive form of the disease is obvious. In other cases the patient makes a partial, but not complete clinical recovery and an interval of some months may elapse before the onset of the progressive type of infection. Some instances of progressive coccidioidomycosis terminate fatally within a few months, but in other cases the patient may live for a year or more. These patients have a continuous low grade fever, marked anorexia and rapid loss of weight and strength. Dyspnea and cyanosis may be extreme as the pulmonary infiltration increases. The sputum is mucopurulent and sometimes bloody and usually contains many of the characteristic fungus spherules. Invasion of the bones, joints, skin, subcutaneous tissues, internal organs, brain and meninges occurs with great regularity. Occasionally coccidioidal meningitis is found in patients who show no evidence of the primary portal of entry.

The progressive form of the disease should be suspected if the shadows found in the primary form persist for more than six weeks. The diagnosis of the progressive form is almost certain if new lesions appear in the chest or if tuberculous-like infiltrations develop in the apical or subapical areas. A progressive increase in mediastinal adenopathy is a bad sign. When progressive coccidioidomycosis is suspected, the entire skeleton should be x-rayed.

The typical lesion in the bones appears as a sharply circumscribed area of destruction with little or no reaction in the surrounding bones. Such lesions are cyst-like in appearance and vary from 0.5 to 3 cm. in diameter. Although any bone in the body may be involved, the ribs, vertebral bodies, small bones of the hands and feet, tibial tubercles, malleoli, olecranon, styloid processes, acromial processes and the angles of the scapulae are most often invaded in the order named. A terminal miliary dissemination to the lungs is not unusual.

The precipitin and complement-fixing antibodies are present in a high titer in progressive coccidioidomycosis, but the coccidioidin skin test frequently becomes negative in the terminal phase of the infection.

Sputum and exudates should be examined directly in 10 per cent sodium hydroxide for the presence of the typical spherules, which are thick-walled structures 20 to 80 μ in diameter containing numerous small endospores 2 to 5 μ in diameter. Sputum and other materials should also be planted on Sabouraud's glucose agar and incubated at room temperature. On this medium the organism develops, after ten days or two weeks, a moist, membranous colony which remains closely applied to the surface of the agar. With further incubation an abundant cottony aerial mycelium appears which is white at first but becomes tan to brown with age. The typical microscopic picture shows the presence of numerous thick-walled, rectangular, ellipsoidal or spherical arthrospores about 2.5 to 3 by 3 to 4 μ in size. These arthrospores are highly infectious; a number of laboratory infections have resulted from their inhalation.

Coccidioidomycosis should be suspected in every obscure illness originating in a person living in an endemic area or in individuals who have visited such areas at any time. Primary coccidioidomycosis may be diagnosed incorrectly as common cold, bronchitis, influenza, bronchial pneumonia or primary atypical pneumonia of unknown etiology. Progressive coccidioidomycosis must be differentiated from tuberculosis, syphilis, glanders, tularemia, bacterial osteomyelitis, neoplasms and other mycoses, particularly blastomycosis, actinomycosis, cryptococcosis, sporotrichosis and mycetoma.

The *prognosis* is excellent in primary pulmonary coccidioidomycosis, and it is good in the cutaneous and glandular types of primary infection. In progressive coccidioidomycosis the prognosis is very grave. The mortality is usually given as 55 to 60 per cent, but it is probably much higher than this since the primary benign type of the disease was not differentiated from the more severe progressive form of the disease in the earlier reports in the literature.

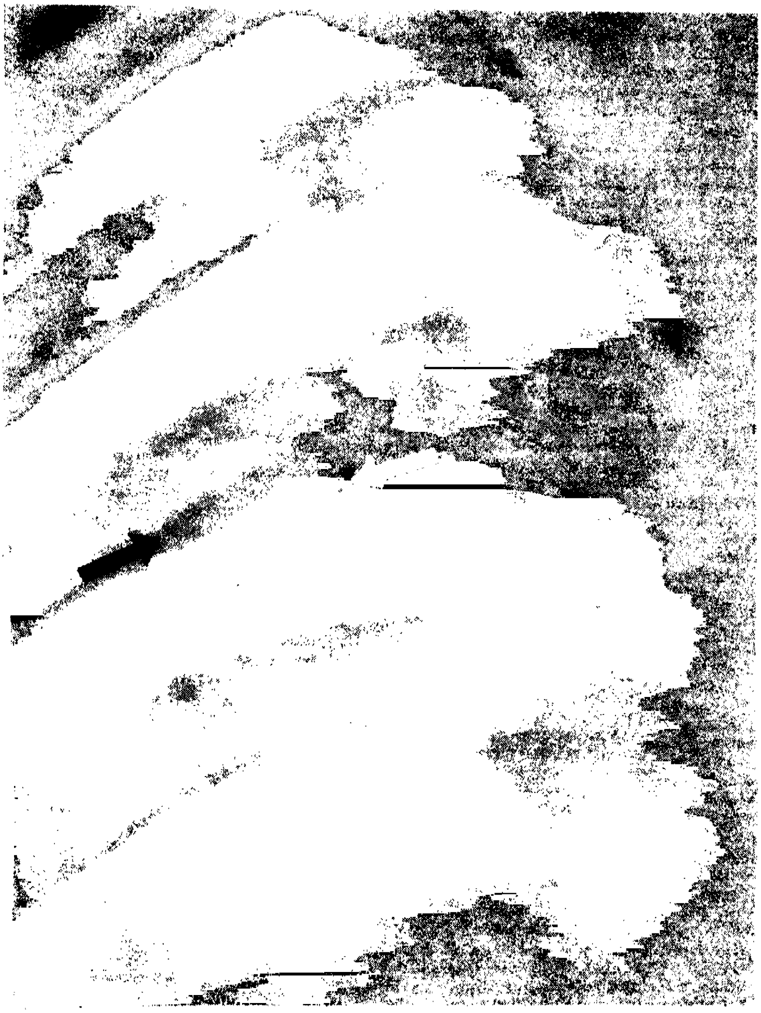

Figure 6. Primary coccidioidomycosis, showing the thin delicate wall of the cavity. The cavity began to close by the 29th day of the disease. After one year there was a cyst-like shadow in the region and one single small nodule in the periphery of the lung; the hilar nodes were much denser, suggesting the possibility of calcification. The patient was clinically well. (After Powers and Starks, *Radiology, 37*: 448, 1941.)

The *treatment* for primary coccidioidomycosis is symptomatic. The patients should be kept in bed until their temperature, white blood count and sedimentation rate are normal and their x-ray films are either normal or showing progressive clearing. The small residual cavities usually heal in less than one year (Fig. 6). The larger cavities, particularly when complicated by repeated hemoptyses, may require lobectomy. Such operations have been performed by Peers *et al.* and by Blades. There is no known specific treatment for progressive coccidioidomycosis. Every effort should be made to support the general resistance of the patient by rest in bed and a good diet supplemented by liver extract and all the known vitamins. With patients showing hypersensitivity to coccidioidin, an attempt should be made to desensitize, taking care to keep the dose below that producng either a local or a generalized reaction. If desensitization can be effected, then potassium iodide therapy might be useful.

CRYPTOCOCCOSIS

Cryptococcosis, caused by *Cryptococcus neoformans* (*Torula histolytica*), may involve the skin and other parts of the body but has a marked predilection for the lungs and for the brain and meninges. The mycosis caused by this fungus generally is referred to in the European literature as blastomycosis or Busse-Buschke's disease. In the American literature we find the term "European blastomycosis" which is used to distinguish cryptococcosis from North American blastomycosis or Gilchrist's disease. In the American literature most instances of the disease will be found indexed as torulosis.

Cryptococcus neoformans has been found in all parts of the world. It has been reported in children less than 10 years of age and in adults of more than 70, but most of the cases have occurred between the ages of 40 and 60. All races seem to be equally susceptible and almost as many females are infected as males.

Benham isolated a number of cryptococci from the skin of normal individuals. Most of these strains were entirely non-pathogenic, but some had a reduced but definite pathogenicity for animals. These studies suggest that cryptococcosis may be derived from an endogenous source in man although cryptococci pathogenic for animals have been isolated from fermenting fruit juices and naturally occurring infections have been observed in animals.

The *symptoms* of primary pulmonary infections are not diagnostic. The patient presents the picture of a subacute infection with low grade fever and mild cough. In some instances there is no sputum; in others, a small amount of mucoid sputum is produced which rarely is blood stained. The lesions may develop in any part of the lungs, and they are frequently bilateral but may be unilateral and confined to one upper lobe (Fig. 7). Dullness and altered breath sounds usually are found, but rales are inconstant except in patients where there is a terminal miliary dissemination to the lungs. The patient may have a mild respiratory infection with minimal signs and symptoms and apparently be on the road to recovery when the infection spreads to the brain or meninges, precipitating the cerebral type of the disease.

In primary pulmonary infections the shadows are often dense, resembling a massive tuberculous lesion or neoplasm. Cavity formation is unusual and the mediastinum rarely is involved. Miliary lesions may be present throughout the lungs following the terminal dissemination of the fungus. Bone lesions may occur, but they are rare in cryptococcosis in contrast to the frequency with which

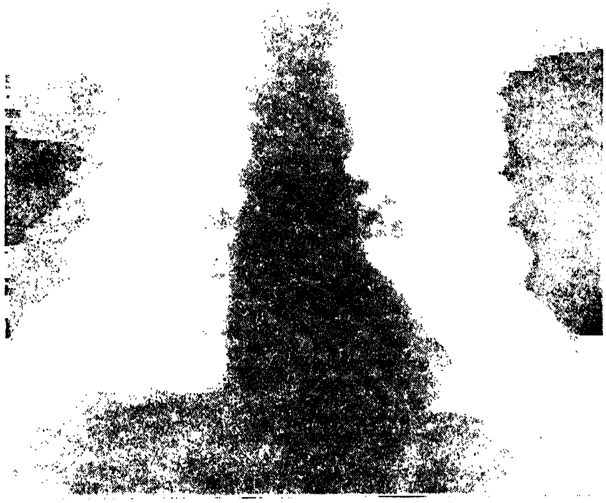

FIGURE 7. Cryptococcosis of the lungs, showing a round, sharply circumscribed mass in the right upper lobe. The lesion subsequently extended and simulated the picture of lobar pneumonia. The patient died after an extension to the brain.

they are found in actinomycosis, North American blastomycosis and coccidioidomycosis.

Although the literature contains an occasional report describing the presence of agglutinating and complement-fixing antibodies in the sera of the infected patients, most observers have failed to demonstrate any serologic evidence of infection. The large mucoid capsule which is characteristic of the appearance of the organism in tissue may inhibit antibody production. Benham was unable to produce agglutinins or precipitins in rabbits by injecton of the whole yeast cells. Antibodies were formed, however, if the animals were injected with cells from which the capsular material had been removed by chemical methods. Positive skin tests to *Cryptococcus* vaccines are rarely obtained.

There is nothing characteristic about the pulmonary symptoms, signs or x-ray pictures of patients with cryptococcosis. The diagnosis of primary pulmonary cryptococcosis usually is made by routine cultures of the sputum on Sabouraud's medium, and this should always be done in every case of obscure pulmonary infection. The organism grows as a soft, creamy white, mucoid colony. When some of the culture is mixed with India ink and examined under the microscope, the large capsule can be seen surrounding the budding yeast cell.

The pulmonary lesions must be differentiated from tuberculosis, other non-tuberculous infections and mycotic infections of the lungs such as actinomycosis, North American blastomycosis, coccidioidomycosis and moniliasis.

The *prognosis* is grave in all forms of cryptococcosis. Most of the primary pulmonary infections have spread eventually to the brain and meninges and produced death. However, it is possible that some of the pulmonary infections may heal spontaneously without the diagnosis ever being established.

Iodides and x-ray have proved of little value in *therapy*. Reeves, Butt and Hammack, in 1941, reported the recovery of one patient after treatment with sulfapyridine, but the authors emphasize that this patient was improving before the drug was given. In 1942, Marshall and Teed cured one case of *Cryptococcus* meningitis with sulfadiazine. We have employed sulfadiazine in two cases of primary pulmonary cryptococcis. One patient showed definite improvement before he developed a sensitivity to the drug; later the infection spread to the brain and death resulted. The other patient tolerated sulfadiazine very well and was clinically well two years after the treatment was stopped. Sulfadiazine should be given in doses sufficient to maintain a blood level of 8 to 12 mg. per 100 c.c. of blood, and the drug should be continued for several weeks after the disappearance of symptoms. In Marshall and Teed's patient several relapses were observed following interruptions in treatment.

Penicillin has been reported as having an inhibiting effect on some strains of *Cryptococcus neoformans* in culture, but confidential reports from several physicians indicate that it is not effective in the treatment of clinical cryptococcosis.

MONILIASIS

A number of species of *Monilia* or *Candida* may be found as normal inhabitants of the mouth and skin. Only *Candida albicans* *(Monilia albicans)* is potentially pathogenic, and even this species may be present as a saprophyte without producing any reaction in the host. *C. albicans* may produce lesions in the mouth, vagina, skin, nails, bronchi or lungs and, occasionally, a septicemia, endocarditis or meningitis. In each instance it must be determined whether the *C. albicans* is the primary cause of the disease or a secondary invader in some pre-existing infection. Moniliasis occurs at all ages, in all races and in both sexes.

Bronchopulmonary moniliasis is the term used to designate that type of *Monilia* infection of the lungs where the disease is confined to the bronchi with a minimum amount of involvement in the peribronchial tissues. The term pulmonary moniliasis is reserved for infections involving the parenchyma of the lungs.

Bronchopulmonary moniliasis is not an uncommon infection. A cough is the most characteristic and distressing *symptom.* The sputum is almost colorless, but mucoid and gelatinous, and frequently contains small gray flakes composed of budding fungous cells and detritus. The temperature is normal or only slightly elevated, and the health of the patient is not affected seriously. The infection sometimes disappears spontaneously but often lasts for years with periodic progressions and retrogressions. The *physical signs* are those of bronchitis with medium and coarse rales at one or both bases of the lungs. A particular type of bronchopulmonary moniliasis occurs in the tea-tasters of Ceylon and has been described in detail by Castellani. The *x-ray films* of patients with bronchopulmonary moniliasis usually show little more than a non-specific type of peribronchial thickening. Sometimes a peculiar hazy type of linear fibrosis can be seen (Fig. 8). Although this picture is not diagnostic, Dr. Robert J. Reeves, of Duke Hospital, often suggests the possibility of moniliasis from the appearance of the film, and cultures very frequently have confirmed his tentative diagnosis.

Pulmonary moniliasis is not as common as the bronchial form but is a more severe disease. There is a moderate elevation of the temperature and pulse, pleural pain is common and effusions occur occasionally. The cough is harassing and the patient produces mucoid, gelatinous sputum which sometimes is blood streaked. When secondary infections occur with pyogenic cocci, the sputum is purulent. The areas of infection are of the lobular or bronchopneumonic type and are frequently scattered in two or more lobes. Occasionally, an entire lobe is involved. Medium moist rales are present over the areas of involvement, but dulness and changes in the breath sounds are variable. In the most severe

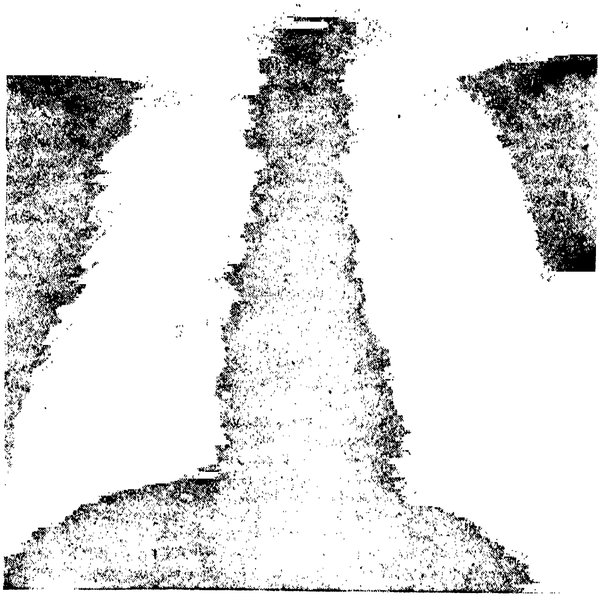

Figure 8. Bronchopulmonary moniliasis, showing diffuse linear shadows and small hazy nodules scattered throughout both lung fields. The patient made a complete recovery following desensitization with an autogenous *Monilia* vaccine, followed by potassium iodide therapy.

infections, the physical signs are those of a confluent or lobar pneumonia with dullness, increased tactile fremitus, whispered voice and prolongation of expiration. The x-ray shadows in pulmonary moniliasis vary in size and shape and resemble those seen in bronchopneumonia except that the edges of the lesions usually are less sharply defined (Fig. 9). Two or more lobes frequently are involved although the apices of the lungs usually are spared.

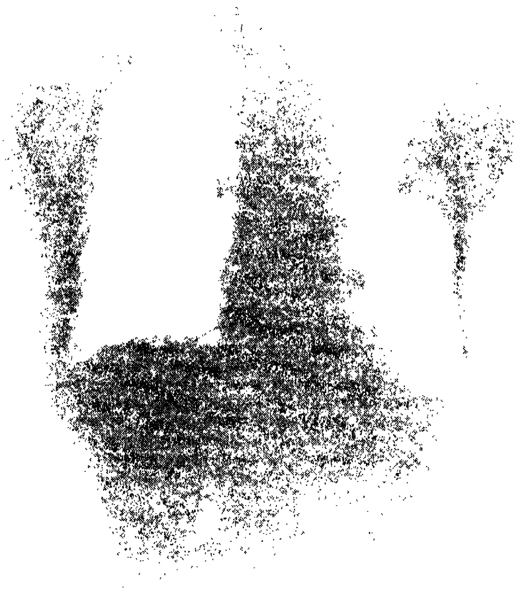

FIGURE 9. Moniliasis of the lungs, showing a homogenous pneumonic shadow in the left upper lobe. The residue of a similar shadow can be seen in the right upper lobe. The patient made a complete recovery after intravenous treatment with gentian violet.

Some lobes may show almost complete consolidation while others contain bronchopneumonic patches. The lesions are very labile, and films made at weekly intervals show definite evidence of clearing in some areas and spreading in others.

Agglutinins have been demonstrated in the sera of patients with moniliasis, and sometimes the titers are as high as 1:2400. They are not constantly present, and we have seen patients with severe infections who had no demonstrable agglutinins in the blood. A large percentage of apparently normal individuals gave positive skin reactions when injected intradermally with vaccines or extracts of *C. albicans.* These findings are not surprising in view of the fact that the fungus is so frequently present on the skin and in the mouths and feces of normal individuals. A positive or negative skin test has little diagnostic value, but skin tests should be performed on all patients with positive cultures for *C. albicans* because the clinical course and management of the individual patient depend, in part, on whether or not the patient is hypersensitive to the fungus.

To establish the *diagnosis* of moniliasis, one should find the budding yeast-like organism by direct examination of sputum or exudates and isolate it in pure culture on Sabouraud's medium. It is necessary to establish the fact that the *Monilia* isolated is the potentially pathogenic *C. albicans.* If agglutinins are present in the patient's serum, we are justified in concluding that the fungus has actually invaded the pulmonary tissues; but agglutinins are not always present, and even when present they may represent the response to a secondary *Monilia* invasion. Every effort should be made to find a primary cause for the pulmonary lesion before accepting *C. albicans* as the etiologic agent. In many instances a definite diagnosis cannot be established without the help of the therapeutic test. If the patient responds to specific treatment and the lesions disappear from the lungs, then we are justifed in concluding that *C. albicans* was probably the cause of the disease.

Bronchopulmonary moniliasis must be differentiated from ordinary bronchitis and the pulmonary form from common pyogenic infections, as well as certain of the mycoses, such as cryptococcosis, blastomycosis, actinomycosis and coccidioidomycosis.

The acute cases of bronchopulmonary moniliasis which do not heal spontaneously develop into the chronic recurring form of the disease which may persist for years. The more severe pulmonary form of the disease runs a shorter course. An occasional patient dies after two or three weeks, but in most instances there is complete recovery after four to six weeks. Occasionally, recovery is not complete and the original pulmonary form of the disease changes over to the more chronic bronchopulmonary form.

Bronchopulmonary moniliasis responds readily, as a rule, to *treatment* with potassium iodide. The iodide should be given by the rapid method described in the section on North American blastomycosis. Ethyl iodide inhalations were employed successfully by MacKee in treating an apparently hopeless case of systemic moniliasis. Before iodides are administered, the patient should be given a skin test with a heat-killed *C. albicans* vaccine to determine the degree of sensitivity to the fungus. Hypersensitive patients should be desensitized before iodides are administered. The dilutions and doses are calculated in the manner described in the section on North American blastomycosis.

Intravenous gentian violet has been recommended by Stovall and others in the treatment of pulmonary moniliasis. The dose of gentian violet is 5 mg. per kilogram of body weight, and it may be repeated daily or every other day for three to seven doses. Undesirable reactions can be avoided if commercially prepared solutions of gentian violet are used, but solutions made in the laboratory are safe if the concentration of the dye does not exceed 0.5 per cent and the solution is filtered through a Berkefeld or a Seitz filter. Thrombosis of the veins may occur in patients who are injected with more concentrated solutions of the dye.

SPOROTRICHOSIS

Sporotrichosis, caused by *Sporotrichum Schenckii,* is a chronic infection with nodule formations in the lymph nodes, skin and subcutaneous tissues which soften and break down to form indolent ulcers.

The disease may develop at any age from 16 months to 71 years but is most common between 20 and 40. About 10 per cent of the cases occur in children. All races are susceptible, males are infected nine times as frequently as females, and the disease is most prevalent in farmers, laborers and horticulturists.

Sporotrichosis is world-wide in distribution. The fungus grows as a saprophyte or as a parasite on certain plants, and spontaneous infections have been observed in horses, dogs, cats, rabbits and rats. Pathogenic sporotricha have been found in the mouth and on the fur of healthy rats, and Meyer recovered it from the coats of healthy horses. Meyer infected himself with a culture isolated from a horse, and Foerster reported two instances of the disease being acquired by handling contaminated dressings from a patient.

Since the classical work of de Beurmann and Gougerot in 1912, the disease usually is described as conforming to one or more of the six different clinical types, namely, (1) lymphatic, (2) disseminated, (3) epidermal, (4) mucosal, (5) skeletal, and (6) visceral. In this country the lymphatic is the predominant type of infection. In the 109 cases collected by Foerster, the initial lesion was on one of the extremities in 90 instances.

Apparently the disseminated form of the disease is seen more frequently in France than in the United States. The epidermal, mucosal, skeletal and visceral forms are relatively rare. Pyelonephritis, orchitis, epididymitis and mastitis have been reported. Pulmonary sporotrichosis is a relatively rare disease, and the critical review by Forbus of the reported cases shows that the evidence was inadequate to justify the diagnosis in most instances. De Beurmann and Gougerot collected six cases from the literature; four they dismissed, but two were accepted as cases of pulmonary sporotrichosis. Since 1912 Forbus has collected four other cases and reported one of his own. In the first of the new cases, reported by Laurent in 1913, *Sporotrichum* was isolated from disseminated lesions, including infections of the bone, but the organism was not grown from the sputum. The pulmonary signs were extensive, and all the lesions of bones, skin and lungs disappeared following treatment with potassium iodide.

In the second case, reported by Dominquez of Havana, Cuba, in 1914, there was some elevation of temperature accompanied by marked malaise, weakness and loss of weight. The physical signs suggested tuberculosis or chronic pneumonia. The chest film resembled an ordinary pulmonary abscess with a well-defined cavity. Large amounts of purulent sputum were produced which were negative for tubercle bacilli but contained filaments of *Sporotrichum,* and the fungus was isolated on artificial media. *Sporotrichum* also was isolated from samples of tobacco with which the patient had been working. After treatment with potassium iodide there was rapid improvement in the clinical conditon of the patient, a marked reduction in the amount of sputum, and the pulmonary shadows decreased to a small wedge-shaped lesion which subsequently completely disappeared. A metastatic lesion of the mastoid cells developed which required operation and more iodide therapy before the patient was entirely well.

The third case was reported by Warfield in 1922. This patient had the disseminated subcutaneous gummatous lesions of sporotrichosis. The chest films showed the right apex to be clear, but the left apex was slightly hazy. Extending out from the right hilum was a large, somewhat circular shadow about 6 cm. in diameter. Radiating from the edge of this solid mass were fine linear markings, extending into the first interspace and outward to the edge of the outer zone. The left hilum was increased in size, and there was some fine spotting along the left border of the heart. The patient died although treated with arsphenamine and potassium iodide. A *Sporotrichum* was isolated from the subcutaneous gummatous lesions during life and from various parts of the body at necropsy. This strain produced nodular lesions in the lungs of albino rats even when the inoculation was subcutaneous. Spores from the *Sporotrichum* were agglutinated by serum from this patient in a dilution of 1:150. Control sera gave no agglutination.

The fourth case was reported by Nicaud in 1926. The patient had an encapsulated mass involving the lungs and pleura, and *Sporotrichum* was grown from material secured by thoracentesis.

The fifth case was reported in detail by Forbus in 1927. For three years the patient had dyspnea on exertion, cough and a moderate amount of mucoid sputum which was occasionally blood streaked. Fifteen months later the x-ray films showed mediastinal shadows suggesting enlarged lymph glands. No tubercle bacilli could be found in the sputum and the tuberculin was negative. The symptoms gradually increased until she had stridor with inspiration and expiration, wheezing and sibilant rales throughout both lungs. By x-ray the shadows had extended from the hilum into the lung fields on both sides. Dr. Charles L. Minor, of Asheville, N. C., suggested the diagnosis of a tracheobronchial adenopathy of mycotic origin. She was restudied at Johns Hopkins where Minor's clinical findings were confirmed and a positive Wassermann discovered. Dr. W. S. Thayer, of Baltimore, followed the case with great interest. He advised treatment with arsphenamine which was not effective and the patient died September 4, 1917. The necropsy was performed by Dr. Admont H. Clark, and *Sporotrichum* was grown in pure culture from the lungs by Dr. Greenspon.

In 1935, Moore and Kile reported a sixth case of generalized sporotrichosis with pulmonary involvement. The x-ray films showed enlargement of the hilar shadows and a fine nodular diffuse infiltration throughout both lung fields (Fig. 10). A pure culture of *Sporotrichum* was isolated from an unopened subcutaneous nodule. The organism could not be grown from the sputum. After two months of iodide treatment there was a marked reduction in the parenchymatous pulmonary infiltration although the hilar shadows were still prominent. The patient was reported as well four months after treatment was started.

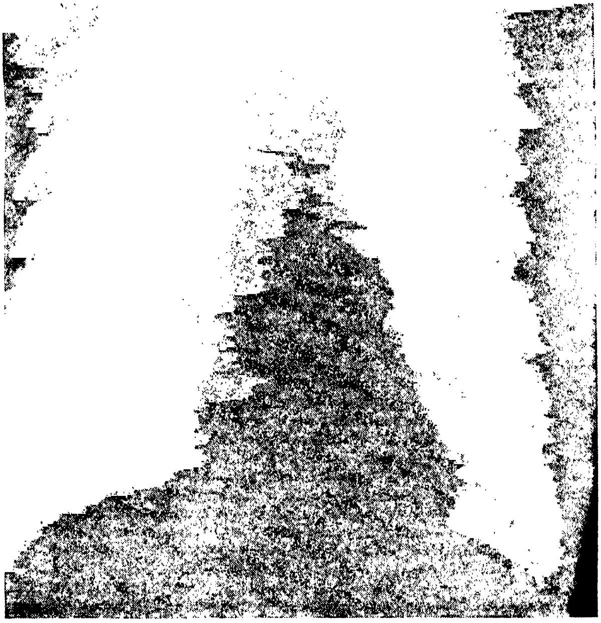

FIGURE 10. Sporotrichosis of the lungs, showing diffuse small nodular shadows throughout both lungs, with some involvement of the hilar lymph nodes. The lesions disappeared following potassium iodide therapy. (After Moore and Kile, *Archives of Dermatology & Syphilology, 31*: 672, 1935.)

We have seen at Duke Hospital one instance where *Sporotrichum Schenckii* was associated with a pulmonary disease. The patient was a child of 10 years, and she presented the clinical picture of asthmatic bronchitis. X-ray films showed enlarged hilar lymph nodes resembling those seen in primary tuberculosis, but she failed to react to an intradermal test with 1 mg. (1:100) of old tuberculin. *Sporotrichum Schenckii* was isolated from the sputum, her blood serum in a dilution of 1:1000 agglutinated a suspension of *Sporotrichum* spores from her culture, and an autogenous vaccine gave a positive skin test of the immediate type.

By 1915 Meyer had collected 400 cases of sporotrichosis from the literature, and several hundred more have been diagnosed since that time. Even if one accepts all nine of the cases referred to above as authentic examples of pulmonary sporotrichosis, this is an astonishingly small number. *Probably all cases of lymphatic sporotrichosis, and certainly all cases of the disseminated disease, should have the lungs studied by x-ray.* Since *Sporotrichum* has a predilection for lymph nodes in other parts of the body, enlargement of the tracheobronchial lymph nodes would be expected. When sputum is present, even though scant in amount and mucoid, it should be streaked over a number of blood agar and Sabouraud's dextrose agar slants, one-half of which should be incubated at 37 degrees C. and the others at room temperature. The tubes should be examined every four days, but should be kept for four to six weeks. The colonies which appear on these initial cultures, especially when bacteria are present, are much smaller than those of other mold-like fungi. The colonies are small, circular in shape, white in color and have a silk-like sheen. There are no aerial mycelia, but short root-like mycelia may penetrate the agar beneath the colony. Recently Campbell has found that the tissue form of *S. Schenckii* can be grown on the glucose cystine blood agar which Francis introduced for the cultivation of *Pasteurella tularense.* It has not yet been determined whether this medium has any advantage over Sabouraud's glucose agar for the primary isolation of the organism.

One cannot question the statement that sporotrichosis of the lungs is a rare disease, but probably it occurs much more often than a review of the literature would indicate. Routine cultures for fungi should be made in all obscure pulmonary diseases and the cultures examined with care at periodic intervals, and from time to time the investigators will be rewarded with an unusual diagnosis——even a case of pulmonary sporotrichosis.

Unfortunately, the growth of a *Sporotrichum* from the sputum will not establish the diagnosis beyond question because the organism is known to occur in vegetable material and has been isolated from the mouths of apparently normal animals. If the patient's serum contains agglutinins for the spores of the *Sporotrichum* of his own culture in a dilution of 1:50 as a minimum or up to 1:1000 or above, the diagnosis is a little more likely. Such patients should be treated intensively with iodides on the assumption that sporotrichosis is the correct diagnosis.

Sporotrichosis must be differentiated from syphilis, tuberculosis, pyogenic infections, glanders, leprosy, tularemia and other types of mycoses.

The *prognosis* is excellent in the lymphatic type but poor with the visceral and pulmonic forms.

Potassium iodide is practically a specific in the *treatment* of sporotrichosis. The initial dose may be 10 drops of a saturated solution t.i.d. p.c. diluted in water or milk, and may be increased by 3 to 5 drops with each of the three daily doses. To avoid recurrences, the treatment should be continued for four to six weeks after apparently complete recovery. Open lesions may be compressed with Lugol's solution. X-ray therapy is indicated as a supplementary treatment for particularly indolent lesions. Vaccine therapy for desensitization may be tried if the response to iodides is unsatisfactory.

HISTOPLASMOSIS

Histoplasmosis was not proved to be a mycosis until about 1934. The etiologic agent, *Histoplasma capsulatum,* causes an infection characterized by emaciation, leukopenia, anemia and irregular pyrexia. There is frequently splenomegaly, hepatomegaly, lymphadenopathy and ulcerations in the naso-oral-pharyngeal cavities and intestines.

The disease has been reported from South America, North America, Central America, England, South Africa, the Philippines and Java. All races seem to be equally susceptible. The youngest patient was one month and the oldest 70 years, but approximately 28 per cent of the cases were in children less than 13 years of age.

Histoplasma capsulatum has not been found in nature, but de Monbreun isolated from a spontaneous infection in a dog a fungus which seems to be identical with strains obtained from patients.

The lungs are rarely, if ever, the site of the primary infection, and only occasionally do they show the most extensive lesions although small lesions usually are present at necropsy from the rather characteristic terminal invasion of the blood stream. Less than 100 cases of histoplasmosis have been diagnosed. Cough has been noted as a symptom in 12 cases, and rales have been heard in the lungs in 14 instances. The lungs showed the most extensive disease in Phelps and Mallory's case, in Meleney's two cases, in Parsons and Zarafonetis' case, in Humphrey's second case and in the recent case of a Negro soldier reported by Colvin, Gore and Peters. In the case of primary histoplasmosis of the knee reported by Key and Large, bilateral symmetrical lesions were found by x-ray in the central two-thirds of both lower lung lobes. Necropsy was refused and the specificity of the pulmonary lesions could not be determined.

More than one-third of the clinical cases of histoplasmosis have

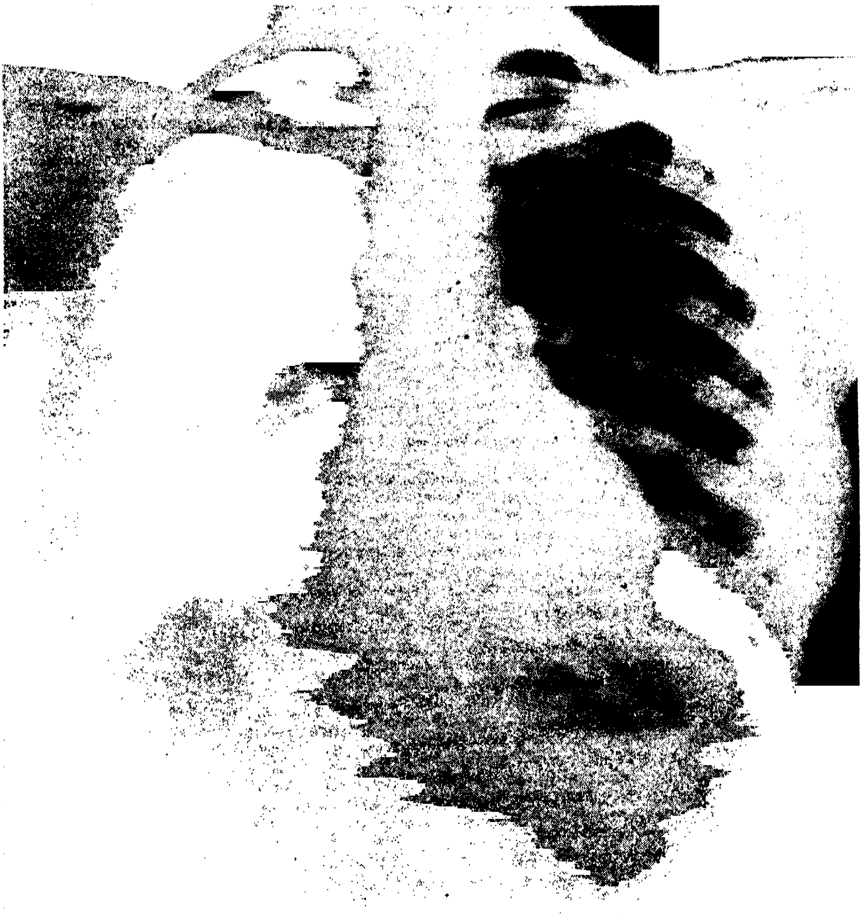

Figure 11. Histoplasmosis, showing calcification in lung fields and in hilar lymph nodes. This film was from a healthy student nurse who had a negative tuberculin and a positive skin test to histoplasmin. (Courtesy of Dr. C. E. Palmer; after Smith, *Clinics, 4*: 1025, 1945.)

been found in the states of Michigan, Missouri, Tennessee and Illinois. Recent studies by Christie and his associates in Tennessee and by Palmer and his co-workers in Kansas, Missouri and Ohio have shown that there is a widespread benign infection throughout the Mississippi Valley area which gives rise to small calcified lesions in the periphery of the lungs with corresponding calcifications in the regional lymph nodes (Fig. 11). These patients give positive skin tests to histoplasmin. In most instances there is no record of a previous clinical infecton of the lungs. Because of the postive skin tests, we suspect that there is a widespread benign form of histoplasmosis which corresponds to the benign form of coccidioidomycosis. At least we can say that there is a widespread infection with either *Histoplasma capsulatum* or an antigenically related fungus. Palmer studied a group of 3,105 student nurses. The pulmonary calcifications in these nurses occurred much more frequently among those who were positive to histoplasmin and negative to tuberculin than among those who were positive to tuberculin but negative to histoplasmin. Christie and Peterson found essentially the same thing in children in Tennessee, and more recently Furcolow, High and Allen studied 16,000 children and 12,000 adults in Kansas City, Missouri. Here again the pulmonary calcifications were twice as frequent among individuals who were histoplasmin-positive and tuberculin-negative than among those who were tuberculin-positive and histoplasmin-negative. Serial studies showed that sensitivity to histoplasmin occurred earlier and developed more rapidly in this group than did sensitivity to tuberculin.

It is tempting to speculate in regard to the surprisingly few instances of progressive pulmonary histoplasmosis in view of the tens thousands of primary pulmonary infections. Perhaps the form of the organism which is inhaled is less virulent than the form which enters the body through the mouth, ears or intestinal tract.

In most of the earlier cases the *diagnosis* was not suspected before necropsy (Fig. 12). The majority of the later cases have been diagnosed ante mortem by biopsy and culture or by cultures from the blood or sternal bone marrow. If sputum is present, smears should be made on coverslips and stained with Wilson's, Wright's or Giemsa's method to demonstrate the small, oval, yeast-like cells which may occur in great numbers in macrophages. The sputum should be cultured on Sabouraud's glucose agar at room temperature for several weeks to develop the characteristic large tuberculate chlamydospores found in the mycelial phase of the fungous growth.

All reports in the literature indicate that histoplasmosis is uniformly fatal. In a few recent necropsies on adults some evidence of healing by fibrosis has been observed, suggesting that limited pulmonary lesions might heal.

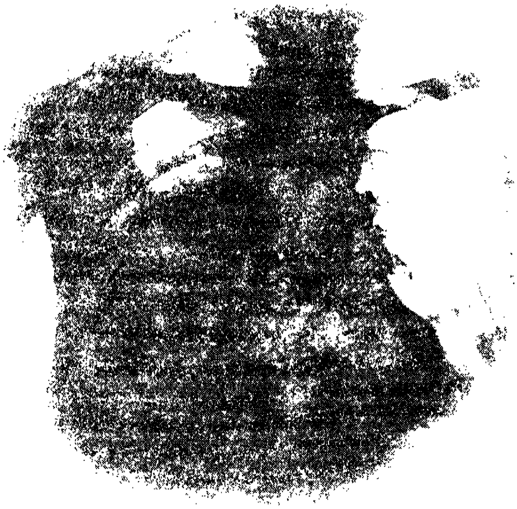

FIGURE 12. Histoplasmosis, showing a dense shadow at the right base with diffuse mottling in the lower portion of the right upper lobe. The necropsy showed enormous numbers of large mononuclear cells completely filled with *Histoplasma capsulatum* although a few tuberculous lesions containing tubercle bacilli were also present in the lungs. (After Meleney, *American Review of Tuberculosis, 44*: 240, 1941.)

Iodides, iodized metals, roentgen radiation, bone marrow extracts, liver extracts, pentonucleotide, neoarsphenamine and sulfonamides have all been tried without effect. Palmer, Amolsch and Shaffer treated one patient with neostam (stibium chloride) and eliminated most of the organisms from the lesions, but the patient died from necrosis of the adrenal glands.

ASPERGILLOSIS, PENICILLIOSIS AND MUCORMYCOSIS

Aspergillus, Penicillium, and *Mucor* are common laboratory contaminants and occur as saprophytic or secondary invaders in a variety of diseases. Occasionally, they are the primary cause of disease in the skin, external ear, nasal sinuses, orbit, bronchi and lungs and sometimes in the bones and meninges.

These common molds are found in all parts of the world. The first fatal case of aspergillosis was reported by Virchow in 1856. Many cases of aspergillosis have been reported in France, particularly in individuals exposed to massive doses of fungous spores, such as (1) squab feeders who take the grain into their mouths to moisten it and incidentally inhale clouds of spores; (2) fur cleaners who use rye flour, containing spores, as grease removers; and (3) agricultural workers exposed to the dust from threshers. Since the beginning of the twentieth century gradually increasing numbers of case reports have appeared in Germany, England, Italy, Australia and North and South America. Pulmonary infections with certain species of *Penicillium* have been reported by Talice and MacKinnon, Nussbaum and Benedek, and Aime, Creuze and Kresser. The case reported by Aime *et al.* presented the clinical and x-ray characteristics of pulmonary abscess.

Several cases of pulmonary mucormycosis have been reported. The first case was studied by Paltauf in 1885; he described the primary infection in the lung, but metastatic abscesses developed in other organs before death. Ernst reviewed the literature in 1918 and reported an additional case from this country. In 1943, Gregory, Golden and Haymaker reported three instances of brain and meningeal infection, presumably due to species of *Mucor* although cultures were not obtained.

Various species of *Aspergillus, Penicillium* and *Mucor* frequently are isolated from the sputum of patients with chronic bronchitis and intrinsic asthma. In most instances they are either accidental contaminants or, at most, secondary invaders. Vaccines prepared from these molds not infrequently give positive skin tests of the immediate type and prove useful as desensitizing agents in chronic bronchitis and intrinsic asthma.

Primary infections with *Aspergillus, Penicillium* and *Mucor* are rare and difficult to diagnose before necropsy. The *symptoms* are similar to those of pulmonary tuberculosis with cough and mucoid or mucopurulent sputum which frequently contains blood. In some instances the general health of the patient is not affected seriously, but in others there is remittent fever, loss of weight, obvious toxemia and the patient slowly becomes cachectic and dies. The physical findings are indistinguishable from those of chronic pulmonary tuberculosis.

In some instances a *marked sensitivity* develops to the antigens of the fungi, and this results in a modification of the clinical picture. Such cases show extensive smooth, patchy shadows in x-ray with a minimum of clinical symptoms, and the shadows tend to clear rapidly, only to reappear in new areas in the lung (Fig. 13). A case of this type has been followed for some years by Dr. Monroe, of the New York State Hospital for Tuberculosis at Ray Brook, N. Y. Dr. Monroe demonstrated the constant presence of the hyphal form of *Aspergillus* in fresh sputum and produced the immediate type of skin test with a vaccine made from the patient's own organism.

Smooth, dense lesions may be present in the lungs and cavity

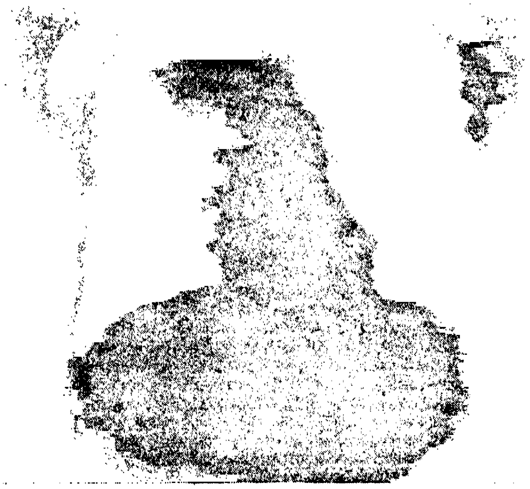

FIGURE 13. Aspergillosis of the lungs, proved by repeated demonstrations of hyphal elements in the fresh sputum. The patient gave an immediate wheal-like reaction to a vaccine made from his own culture. (Courtesy of Dr. H. A. Bray, New York State Hospital for Incipient Tuberculosis, Ray Brook, N. Y.; after Conant *et al., Manual of Clinical Mycology*, W. B. Saunders Company, Philadelphia, 1944.)

formation is frequent. Less commonly the lesions are nodular and diffuse. Sayers and Meriwether found hundreds of examples of a peculiar miliary calcification in the Midwest of the United States in farmers and laborers who had worked in the *Aspergillus*-laden dust around wheat threshers. It has been assumed that the *Aspergillus* produced first a type of localized patchy pneumonia which eventually became calcified (Fig. 14).

The *diagnosis* of bronchial or pulmonary aspergillosis, penicilliosis and mucormycosis cannot be made without repeated demonstrations of branching hyphae in the sputum. The cultivation of the fungus is not sufficient. Since pulmonary aspergillosis, penicilliosis and mucormycosis occur not infrequently as secondary infections in tuberculosis, bronchiectasis and carcinoma of the lungs, these conditions must be excluded before the possibility of primary pulmonary aspergillosis, penicilliosis or mucormycosis can be considered. These infections simulate tuberculosis closely and may be confused with mycoses of other types.

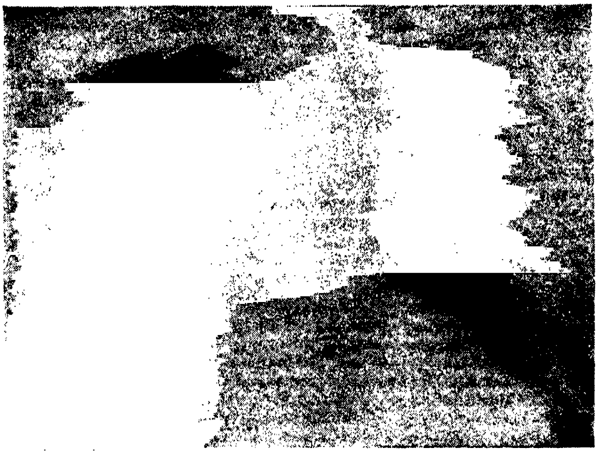

FIGURE 14. Miliary calcification of the lungs found in an Oklahoma wheat farmer, presumably due to a healed aspergillosis. The significance of these calcifications must be re-evaluated in view of the strikingly similar lesions found in primary histoplasmosis. See FIGURE 11. (Courtesy of Dr. M. McConkey, New York State Hospital for Incipient Tuberculosis, Ray Brook, N. Y.)

The *prognosis* is good in mild cases which are limited largely to the bronchi, but is poor when there is massive involvement of the parenchyma of the lung with abscess formation.

Potassium iodide is employed in the *treatment* of aspergillosis, penicilliosis and mucormycosis and may be administered by either the slow or the rapid method as described in the sections on actinomycosis and North American blastomycosis respectively. If the patient is allergic to his own organisms, he should be desensitized before the administration of iodides, as outlined in the chapter on blastomycosis.

CONIOSPORIOSIS

A peculiar type of pneumonitis has been found in lumbermen in the northern forests who are exposed to the spores of *Coniosporium corticale* which grow on the inner bark of dead maple logs. The primary inhalation causes no symptoms, but after repeated inhalations 10 to 20 per cent of the lumbermen develop a pneumonic reaction in their lungs with severe constitutional symptoms. The lesions disappear with rest in bed after three or four weeks. The pneumonitis recurs when the patient again breathes in the spores. This disease has been studied by Towey, Sweany and Huron These investigators have reproduced the disease in guinea pigs by forcing the pigs to inhale the offending spores. This seems to be an example of an allergic pneumonia, and there is no evidence that the fungus actually grows in the pulmonary tissues.

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THIS BOOK

FUNGUS DISEASES of the LUNGS

By DAVID T. SMITH, M.D.

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